Citation:

Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr.* 2008; 87 (2): 339-346.

PubMed ID: 18258623

Study Design:

Prospective cohort

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

The purpose of this study was to examine the association between a low-carbohydrate diet, using a low-carbohydrate diet score and the risk of type 2 diabetes using female participants from the Nurses' Health Study.

Inclusion Criteria:

- Members of the Nurses' Health Study
- Participants were followed from 1980 to 2000.

Exclusion Criteria:

Women at Nurses' Health Study baseline:

- Who left 10 or more food items blank on the semi-quantitative food-frequency questionnaire
- With very high or very low intakes, defined as more than 3,500kcal or less than 500kcal, respectively
- With a history of diabetes, cancer (not including non-melanoma skin cancer) or cardiovascular disease at baseline because of usual dietary alterations associated with the disease.

Description of Study Protocol:

Recruitment

Members of the Nurses' Health Study who met the inclusion and exclusion criteria.

Design

- One cohort of female registered nurses aged 30 years to 55 years old completed a mailed

questionnaire at baseline
- Information on disease status and lifestyle factors was collected every two years, including the use of post-menopausal hormones, smoking status, body weight and physical physical activities
- Diet was assessed by an SFFQ every four years:
    - A dietary assessment was used and broken down into nutrient values for carbohydrate, total fat, protein, trans fat, saturated fat, polyunsaturated fat and cereal fiber
    - The participants were divided into deciles according to fat, protein and carbohydrate intakes. Those with the *highest* protein and fat scored 10; those with the *lowest* carbohydrate intake scored 10. Macronutrient scores were summed to create the low-carbohydrate-diet score, which ranged from zero (low protein and fat, high carbohydrate) to 30 (high protein and fat, low carbohydrate). Women were divided into deciles based on this low-carbohydrate-diet score.
- The outcome measured was the occurrence of type 2 diabetes mellitus
- Relative risk (RR) of type 2 diabetes by decile was calculated for total low-carbohydrate score, animal low-carbohydrate score and vegetable low-carbohydrate score
- Relative risk was further stratified according to macronutrient consumption to look for significance.

Statistical Analysis

- Incidence rates for type 2 diabetes were calculated by dividing cases by person-years of follow-up for each decile of low-carbohydrate-diet score
- Relative risk (RR) of type 2 diabetes was calculated by dividing the rate of occurrence of type 2 diabetes in each decile by the rate in the first (lowest) decile
- Cox proportional hazards models adjusted for potentially confounding variables, including body mass index, family history of diabetes, smoking, alcohol use, post-menopausal hormone use and physical activity
- Used multivariate nutrient density models to examine the association between each macronutrient and risk of type 2 diabetes
- Also explored the association between dietary glycemic load and the risk of type 2 diabetes
- All P-values were two-sided
- Tests for trend used the median value for the category of low-carbohydrate-diet score, which was examined as a continuous variable in regression models.

Data Collection Summary:

Timing of Measurements

- Dietary assessment using SFFQ: Every four years, beginning in 1980
- *Non-dietary factors*
    - Family history of diabetes in first-degree relatives was provided in 1982 and 1988
    - Information on use of post-menopausal hormones, smoking status and body weight was provided every two years
    - Specific weekly physical activities were self-reported in 1980, 1982, 1986, 1992, 1996 and 1998
        - Average number of hours per week spent in moderate or vigorous activity was calculated.
- Each participant was followed until death, self-report of type 2 diabetes or the end of the study in June of 2000.

Dependent Variables

- Incidence of type 2 diabetes mellitus
  - Measured by self-reported diagnosis of diabetes
  - Followed-up with a supplementary questionnaire regarding symptoms, diagnostic testing and treatment. A diagnosis of type 2 diabetes was defined by having at least one of the following, according to criteria from the National Diabetes Data Group:
    - At least one classic symptom (excessive thirst, polyuria, hunger or weight loss) plus a fasting plasma glucose concentration of at least 140mg per dL or a random plasma glucose concentration of at least 200mg per dL
    - At least two elevated plasma glucose concentrations on different occasions (fasting at least 140mg per dL, random at least 200mg per dL or random at least 200mg per dL after at least two hours of oral-glucose-tolerance testing in the absence of symptoms
    - Treatment with hypoglycemic medications.

Independent Variables

- Low-carbohydrate score: Ranged from zero (lowest fat and protein intakes and highest carbohydrate intake) to 30 (highest protein and fat intakes and lowest carbohydrate intake)
- Glycemic load: Calculated by multiplying the carbohydrate content of each food by its glycemic index and then multiplying this value by the frequency of consumption
- Macronutrient intakes: SFFQ used 61 food items, revised to about 120 items in subsequent cycles. Reported frequency of consumption with a commonly-used portion size and baseline and throughout the previous year. Intakes of specific foods:
  - Nutrient values of foods were computed by multiplying the frequency of consumption of each food by the nutrient content of the portion and adding products across food items
  - Food composition values were from the Harvard University food-composition database, which was derived from US Department of Agriculture sources.

Control Variables

Used Cox proportional hazards to adjust for confounding variables: Body mass index, family history of diabetes, smoking, alcohol use, post-menopausal hormone use and physical activity.

Description of Actual Data Sample:

- *Initial N:* 85,059 (all female)
- *Attrition (final N):* 85,059 (all female)
- *Age:* 30 years to 55 years old at baseline recruitment questionnaire in 1976
- *Ethnicity:* 98% Caucasian; other ethnicities not noted
- *Other relevant demographics:* Data not specifically noted, however most participants noted to have "some college education"
- *Anthropometrics:* No significant differences noted across groups with regard to family history of type 2 diabetes, body mass index, post-menopausal hormone use, physical activity, trans fat or total calories
- *Location:* Surveys from the United States.

Summary of Results:

Key Findings

- Documented 4,670 cases of type 2 diabetes
- No association between low-carbohydrate-diet score and risk of type 2 diabetes in either obese or non-obese women
- No evidence of effect modification of the relation between low-carbohydrate diet score and type 2 diabetes when stratified by smoking status, family history of type 2 diabetes or physical activity
- The multivariate risk (RR) for diabetes, after adjustment for covariates and BMI, comparing the highest and lowest decile of low-carbohydrate-diet score, was 0.90 (not significant) and for the low-carbohydrate score (animal protein and fat) was 0.99 (not significant)
- The multivariate risk (RR) for diabetes, after adjustment for covariates and BMI, comparing the highest and lowest decile of low-carbohydrate-diet score (vegetable protein and vegetable fat) was 0.82 (P for trend =0.001)
- Multivariate relative risk of diabetes for the comparison of extreme deciles of low-carbohydrate-diet score according to macronutrient consumption was significant for:
    - Carbohydrate (P=0.003)
    - Glycemic load (P<0.0001)
    - Vegetable fat (P<0.0001).
- General outcome end-point of type 2 diabetes diagnosis: Documented 4,670 cases of type 2 diabetes
- Baseline characteristics:
    - In 1980, the mean low-carbohydrate-diet score was 18.2±7.2
    - Women who had higher low-carbohydrate dietary score tended to have a lower dietary glycemic load, lower cereal fiber, refined grain, and fruit and vegetable intakes and higher red meat, animal fat and saturated fat intakes
    - Family history of type 2 diabetes, body mass index, post-menopausal hormone use, physical activity, trans fat and total calories were not significantly different across deciles.
- Stratified analysis (data not shown)
    - No association between low-carbohydrate-diet score and risk of type 2 diabetes in either obese or non-obese women
    - No evidence of effect modification of the relation between low-carbohydrate diet score and type 2 diabetes when stratified by smoking status, family history of type 2 diabetes or physical activity.

Relative Risk (RR) of Diabetes, According to Low-Carbohydrate Diet Score

	RR	CI	P for Trend
Low-Carbohydrate Diet Score (Total)*	0.90	0.78, 1.04	0.26
Low-Carbohydrate Diet Score (Total), Age Adjusted RR Only	1.40	1.21, 1.61	<0.0001
Low-Carbohydrate Diet Score (Animal Protein + Fat)*	0.99	0.85, 1.16	1.0

Low-Carbohydrate Diet Score (Vegetable Protein + Fat)*	0.82	0.71, 0.94	0.001

*Adjusted for multivariate variables (adjusted for age, smoking, post-menopausal hormone use, physical activity, alcohol intake, and family history of type 2 diabetes in a first degree relative, and BMI)

Multivariate Relative Risk of Diabetes for the Comparison of Extreme Deciles of Low-Carbohydrate-Diet Score, According to Macronutrient Consumption

	RR: Decile 10	CI	P for Trend
Carbohydrate	1.26	1.07, 1.49	0.003
Glycemic Load	2.47	1.75, 3.47	<0.0001
Vegetable Fat	0.74	0.62, 0.89	<0.0001

Author Conclusion:

- In a large prospective cohort of Caucasian women, a higher low-carbohydrate-diet score was not significantly associated with risk of type 2 diabetes after adjustment for confounding variables
- Diets high in vegetable fat and protein may somewhat reduce the risk of diabetes.

Reviewer Comments:

- *Researchers also looked at the correlation between the expanded food-frequency questionnaire and two one-week dietary records and which was 0.64 for carbohydrate, 0.57 for fat and 0.50 for protein, which seems to be low. However, the reviewer is unaware of the general level of correlation of such questionnaires to weekly intakes. This was not addressed in the discussion of results, except to say that some misrepresentation likely occurred, but was minimized by the number of questionnaries and length of the study.*
- *Confirming the diagnosis of diabetes from the supplemental questionnaire was highly reliable. In a random sample of women, endocrinologists reviewed the medical records and confirmed the diagnosis by questionnaire in 98% of cases.*
- *A change in the diagnosis criteria for type 2 diabetes in 1997 by the National Diabetes Data Group lowered the fasting glucose concentration to at least 126mg per dL. In 1998, the study switched to using the American Diabetes Association criteria for the remainder of the study.*
- *Calculated a 5.5% incidence of type 2 diabetes based on the baseline N of 85,059 subjects*
- *Sample is characteristic of the population at the time (female US registered nurses in 1976); further ethnicities should be studied.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes

3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	N/A
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes

6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	Yes
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	N/A
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes

9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes